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Estimating attributable fraction of mortality from sepsis to inform clinical trials

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Running heading: Attributable fraction of sepsis for trial design

Abstract

Purpose:

Nearly all sepsis trials report no statistically significant difference in mortality. The attributable fraction of deaths due to sepsis (AFsepsis) may be an important, yet overlooked consideration. We derived AFsepsis and explored the effect of incorporating AFsepsis into sample size calculations.

Materials and Methods:

We derived AFsepsis with a matched cohort study using consecutive admissions to adult general intensive care units (ICUs) in England (n=614,509). Cases were ICU patients with sepsis and the two controls were ICU-non-sepsis controls, matched for propensity to have sepsis and age-sex-matched general population. The primary exposure was sepsis. The primary outcome was hospital mortality. We generated sample size graphs, by varying control group mortality (10%-60%), relative risk reduction (0-1), for 80% power and 5% alpha. We then compared AFsepsis derived sample sizes with sample size calculations from published sepsis trials.

Results:

AFsepsis was 15%(95%CI:14%-16%) compared with propensity matched ICU-non-sepsis controls and 93%(95%CI:92%-93%) compared with age-sex-matched general population controls. When comparing AFsepsis derived sample sizes with sample size calculations from 18 trials meeting our selection criteria, these calculations assumed very high AFsepsis and/or very effective treatments.

Conclusions:

Estimating trial specific AFsepsis to inform sample size calculations could be an additional step in sepsis trial design.

Key words: Sepsis; Attributable fraction; Randomized Controlled Trial; Sample size

Introduction

Sepsis [1] is common and is associated with a hospital mortality of 18% to 33% [2]. Numerous sepsis randomized clinical trials (RCTs) that do not demonstrate a statistically significant difference in the primary end point [3] may be explained by treatment response variations seen within trial populations [4-7] and differences in sepsis pathobiology [3, 8]. In addition to identifying novel, more effective therapies, there may be opportunities during design to improve the sensitivity of RCTs [9]. These trial design modifications have generally focused on enrolling sepsis patients at high risk of death, accounting for risk of death in the analysis, excluding patients with, for example, cancer or cirrhosis, whose risk of death is due to their comorbidity, or enriching the population with patients susceptible to the intervention based on its mechanism [6, 9].

In this paper, we present a novel analysis of sepsis RCTs using the attributable fraction of deaths due to sepsis (AFsepsis) approach [10, 11]. The hypothesis is that risk factors for sepsis including age, sex and comorbidities are also risk factors for death in critically ill patients regardless of the aetiology of their critical illness. If only deaths in the attributable fraction are preventable with a sepsis therapy and this fraction is less than 100%, larger sample sizes may be needed to detect plausible treatment effects.

Materials and Methods

Conceptual approach

The interventions tested in sepsis RCTs are developed based on dominant biological pathways observed in sepsis [3]. The interventions' ability to reduce risk of death is defined using either absolute or relative risk reduction (RRR). The standard approach for sample size estimation in RCTs assumes a RRR across 100% of

deaths with the disease. If the control group mortality in a sepsis RCT is 40% and we expect the drug to have 20% RRR, then treated patients will have a mortality of 32% and 564 patients per group would be required with typical assumptions of 80% power and 5% alpha to detect this effect. The AFsepsis approach explores the possibility that, for illustration, only 50% of deaths are attributable to sepsis and assumes that only these deaths are affected by treatments for sepsis and that there are no placebo responders [10]. If the RRR of 20% applies only to the attributable deaths, the *effective RRR* would reduce to 10% and will require 2311 patients per group in this RCT. After empiric estimation of AFsepsis, we compared the sample size estimates between the standard and the AFsepsis approach across a range of AFsepsis, control group mortalities and treatment effectiveness amongst attributable deaths (effective RRR) using examples from published sepsis RCTs [12, 13]. Although intuitive and often discussed, the attributable mortality from sepsis-related critical illness has not been estimated for Sepsis-3 criteria [1, 14], whilst attributable mortality and morbidity estimates from ICU acquired infections highlight that these may be quite low [15-17].

Study design and data source

We performed a matched cohort study with cases that met *Sepsis-3* criteria [1] (eTable1 [18]) and controls that were either non-septic critically ill patients or general population to estimate the range of AFsepsis. For sepsis cases and non-septic critically ill controls, we used the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme Database (CMPD) [19] (Further details are reported in eMethods).

Rationale for controls

Estimating the attributable risk of sepsis requires careful selection of controls and attention to confounding variables. We attempted to estimate the bounds of AFsepsis and AFseptic shock by using general population and non-septic critically ill controls. Population controls will estimate the upper bound of the AFsepsis as they reflect the best-case scenario that a treatment returns patients admitted to the ICU with sepsis to the mortality that patients of similar age and sex would incur. Since unmeasured risk factors for sepsis in the population are also predictors of mortality[20], this assumption is optimistic. The non-septic critically ill controls will estimate the lower bound of the AFsepsis as they reflect a worst-case scenario that a treatment returns patients admitted to the ICU with sepsis to the mortality that non-septic *critically ill* patients of similar age, sex, comorbidity and surgical status would incur. Since non-septic critically ill controls incur mortality risk for unique reasons due to their reason for ICU admission and severity of illness, this estimate of AFsepsis is likely to be an under-estimate. Therefore, while it is unknown whether an effective sepsis therapy will return patients to a mortality trajectory similar to the population at large or to a general ICU population, we believe that the AFsepsis likely falls in this range. This approach to estimate bounds of AFsepsis is similar to that used for estimating the magnitude of cardiovascular events in sepsis survivors [21].

Analyses

The primary exposure was sepsis. The primary outcome was acute hospital mortality. All analyses presented as 'sepsis' included the subpopulation with septic shock. In Sepsis-3 definitions, as septic shock is considered a subset of sepsis with greater risk of death than sepsis alone[14], we replicated all the analyses for this

subpopulation. Amongst the 654,918 ICU admissions, we excluded patients with readmissions (0.05%), patients with missing data on acute illness severity (3.9%), and acute hospital mortality (0.3%), resulting in a cohort of 614,509 ICU admissions for complete case analyses (eFigure1).

Estimating AFsepsis and rationale for propensity matching

Propensity-score methods can be used in a matched cohort study design, to estimate the causal effects of sepsis by balancing sepsis and non-septic controls on a set of observed baseline covariates [11, 22]. To estimate the mortality of non-septic critically ill patients we identified a population [similar to sepsis](#) based on a propensity model with age, sex, severe comorbidity defined using Acute Physiology And Chronic Health Evaluation (APACHE II method), and surgical status, assuming AFsepsis is constant across different baseline risks [10, 11]. Since the overall goal was to estimate the independent risk of death attributable to sepsis, we did not incorporate acute physiologic derangement which likely mediates the effects of sepsis on hospital mortality. Further details of propensity methods and rationale for sensitivity analysis to estimate AFsepsis and AFseptic shock are reported in e-methods.

For population controls, age- and sex-specific expected probabilities of death for the general population of England in 2014 were obtained from the Office for National Statistics [23]. We used the shortest timeframe available, one-year risk of death, to estimate the hospital mortality that could be expected by a treatment that reduced AFsepsis to age- and sex-matched population norms.

Comparing AFsepsis based sample size estimates to standard approach

In sepsis RCTs, as all patients have the exposure sepsis, AFsepsis could be used for sample size estimations [10]. We derived sample sizes for the estimated

range of AFsepsis [10], by varying the expected control group mortality between 10% and 60%, the effective RRR between 0 and 1, for typical assumptions of 80% power, 5% alpha and their corresponding constants from normal distribution.

For illustrating how change in AFsepsis within a trial population could influence power and sample size calculation of trials, we identified parallel group sepsis RCTs, published since 2007, testing a single intervention, with mortality as the primary outcome and included in two recent meta-analyses [12, 13]. We chose parallel group RCTs, as there are additional assumptions involved in other RCT designs for sample size calculations [24]. We explored patterns of inclusion and exclusion criteria used in these RCTs. We then extracted control group mortality, RRR, power and alpha that informed standard sample size calculations from these RCTs for exploring the impact of AFsepsis estimations. If trials used absolute risk reduction, then the corresponding RRR was derived.

Reported p values are two-sided and p values less than 0.05 were considered statistically significant. All analyses were performed using Stata/SE version 14 (StataCorp LP, College Station, TX).

Results

Patient characteristics

Amongst 614,509 ICU admissions with 179,717 sepsis and 36,838 septic shock cases, we matched 179,704 sepsis and 36,833 septic shock cases to ICU-non-sepsis controls, propensity score balanced on age, sex, severe comorbidity and surgical status. Sepsis patients had a greater risk of death compared to propensity matched non-sepsis ICU controls (hospital mortality 32% vs 27%; risk ratio 1.18; 95% CI (1.17% - 1.19%); $p < 0.001$). Similarly, septic shock patients had a greater risk

of death compared to propensity matched non-sepsis ICU controls (hospital mortality 56% vs 28%; risk ratio 1.99; 95% CI (1.95 - 2.03); $p < 0.001$) (Figure-1 and Table-1).

Range of AFsepsis and AFseptic shock

Using ICU-non-sepsis controls, AFsepsis was 15.2% (95%CI 14.4%-16.1%) and AFseptic shock was 49.8% (95%CI 48.8%-50.7%). Compared with age- and sex-matched general population controls, AFsepsis was 92.5% (95%CI 92.3%-92.7%) and AFseptic shock was 94.6% (95%CI 94.3%-94.9%) (Figure-1).

Sepsis patients without comorbidities had a greater risk of death compared to propensity matched non-sepsis ICU controls without comorbidities (hospital mortality 29% vs 24%; risk ratio 1.18; 95% CI (1.16 - 1.19); $p < 0.001$) and the AFsepsis was similar to the overall sepsis population 15.0% (95%CI 13.9%-15.9%). Septic shock patients without comorbidities had a greater risk of death compared to propensity matched non-sepsis ICU controls without comorbidities (hospital mortality 52% vs 25%; risk ratio 2.12; 95% CI (2.07 - 2.17); $p < 0.001$) and the AFseptic shock was also similar to the overall septic shock population 52.8% (95%CI 51.7%-53.9%). In the posthoc sensitivity analysis estimating AFsepsis and AFseptic shock excluding patients with active treatment withdrawn 12 hours of ICU admission, we observed a small increase in AFsepsis to 17.2% (95% CI: 15.7% – 18.9%) and small decrease in AFseptic shock to 44.5% (95% CI 42.6% – 46.4%), when compared to primary analysis (eTable-2).

Comparing AFsepsis based sample size estimates to standard approach

Amongst the trials included in the two systematic reviews [12, 13], 18 RCTs met our inclusion criteria (eTable3 and eTable4). Trial inclusion criteria had infection, two or more systemic inflammatory response syndrome and organ dysfunction as key inclusion criteria. The exclusion criteria varied in trials and could be categorized

into generic (such as unlikely to survive beyond 24 hours) and intervention specific (such as coagulopathy) (eTable3). For sample size calculations in these RCTs, the median (interquartile range) control group mortality used was 44% (37% - 50%) and RRR was 20% (20% - 38%). Most trials aimed for 80% power and 5% alpha. The sample size per group varied between 64 to 800 patients (eFigure2 and eTable4). At AFsepsis=93%, the effective RRR is very similar to the RRR used in the sample size calculations. At AFsepsis=15% and AFsepsis=54%, the effective RRR is reduced to that fraction of the RRR used for sample size estimates and significantly reduces the statistical power of these trials (Figure-2). For any fixed combinations of control group mortality and effective RRR, the sample size will decrease with increase in AFsepsis (Figure-3). Similarly, for any AFsepsis value, the sample size will decrease with increase in effective RRR (Figure-3). Higher the control group mortality, lower will be the sample size for any combination of AFsepsis and effective RRR (Figure-3).

Discussion

We show that AFsepsis in critically ill patients varies between 15% and 93% and the higher AFseptic shock is consistent with greater risk of death subset highlighted by Sepsis-3 definitions [14]. As AFsepsis is likely to be less than 100% even with the best case-scenario, our analyses illustrate that existing RCTs could be considered as underpowered except when most deaths are attributable to sepsis, and the treatment is extremely effective, under the key assumption that only AFsepsis deaths are affected by treatments for sepsis. The key interpretation and value of our methodological study is that, accounting for AFsepsis in trial populations could to improve the sensitivity of future sepsis RCTs.

All RCTs have inclusion and exclusion criteria, which serves to identify patients with the illness and specifically exclude patients who are either unlikely to benefit or have a greater likelihood of harm from the trial treatment [9, 25]. The sepsis RCTs mainly differ in terms of their exclusion criteria (eTable-3) [26], with similar inclusion criteria [27]. Therefore, we do not suggest that these principles are completely ignored in published sepsis trials where, for example, patients with metastatic cancer and cirrhosis are frequently excluded presumably because of the high non-sepsis attributable mortality of critical illness in these subsets (eTable-3) (20).

Our analysis highlights the need for explicitly estimating trial specific AFsepsis to inform sample size calculations. The challenge is to determine the comparator population for these estimations. For example, the intervention could *either* reduce the risk of death from sepsis to those experienced by similar patients with the same site of infection but without organ dysfunction (such as uncomplicated urinary tract infection) *or* the intervention would counteract all the effects of the sepsis state, returning the patient their pre-sepsis health state. The control group chosen should match the target state of the treated patient population the intervention is expected to achieve and the trial objectives (Table-2).

The AFsepsis approach complements other recent recommendations about trial design including susceptibility to tested treatment and likelihood of outcome [6, 9], by identifying, empirically, patients at the greatest risk of dying from sepsis. Identifying patients with a mechanism that is responsive to the tested intervention is referred as predictive enrichment, with the assumption that the target biological effect of sepsis is a major contributor for death. This principle has been demonstrated using the association between mortality and response to PEEP in

Acute Respiratory Distress Syndrome patients [28] and for corticosteroid responsiveness in septic shock [29]. These methods are particularly challenging in critical care, as markers of treatment response that are in the causal biological network[30] of the tested intervention and independently associated with higher mortality, are difficult to ascertain. For example, intravenous immunoglobulin (IVIg) trials test effects of immunomodulation and normalisation of low immunoglobulin levels in sepsis, with no consistent benefits [31]. However, enriching on low immunoglobulins alone may not overcome this [32], but enriching a sepsis population with combination of low immunoglobulin levels alongside raised free light chains implying impaired immunoglobulin production, might[33]. Prognostic enrichment, which uses the risk of the study outcome as predicted by baseline covariates, relies on the observation that treatment effects usually exert a fixed relative risk of benefit regardless of the individual patient's risk of the outcome. Patients at the greatest risk of the outcome derive the greatest, and therefore, the easiest to measure, benefit[34]. This method was tried, unsuccessfully, in the evaluation of activated protein C in patients with both low[35] and high risk of death[36]. More sophisticated approaches to incorporating baseline risk of outcome in to trial design have been proposed[37]. We also show how the baseline risk of death is also important as patients at the highest risk of death also have the highest AFsepsis (see Figure-3).

Our study has strengths and limitations. We estimate AFsepsis for the first time using the Sepsis-3 criteria. We report an AFsepsis range using two control populations. The upper limit of the range highlights that AFsepsis is unlikely to be 100% as similarly ill patients have high mortality even when not septic because sepsis, unlike, say myocardial infarction, does not usually occur in previously healthy

patients. We used a high-quality representative national database that had enough patients to use a strict 1:1 matching criteria and matched >99% of the sepsis cohort to non-sepsis ICU controls to reduce confounding in the sepsis and mortality association. We then used AFsepsis to generate isopleths of control group mortality for different RRR to illustrate the impact of knowing AFsepsis during trial design, which is novel. Although we have highlighted the AFsepsis conceptual principles using original data, with two different controls and propensity methods, we have not formally tested this in a completed trial. Despite our use of a multivariate propensity model, residual confounding is certainly a concern. Failure to account for residual confounders might make the estimated AFsepsis even smaller than estimated in this study. Our analysis uses ICU controls and these controls might have higher mortality than hospital based non-septic controls, due to their underlying illness. Our analysis is relatively robust to this concern as we did not incorporate acute physiologic derangement in our propensity score, however, a theoretic sepsis therapy that might avoid ICU admission entirely would need an AFsepsis analysis using hospital non-septic controls (Table-2). Despite this limitation, our analyses are consistent with the AFsepsis estimates of ICU acquired secondary sepsis that yielded attributable fractions between 10.9% and 21.1%[15], and ventilator associated pneumonia attributable fraction between 4.4% and 13%[16, 38].

Our analysis raises a number of important future studies. First, as magnitude of sepsis-related mortality is influenced by the site of infection, organ dysfunction characteristics and the end point chosen in trials (such as 28-days or 90-days), the trial specific AFsepsis is also likely to vary [14, 39]. Like baseline risk of death, there is likely to be a heterogeneity of AFsepsis within any given trial population and lends itself to similar analytic solutions [5]. Our analysis highlights the need to reconsider

the expected magnitude of RRR chosen for sample size calculations in sepsis trials. Given the potentially large sample size requirements, when either the AFsepsis is low or the likely RRR in a trial population is low, we illustrate the need for efficient trial designs in critically ill patients to prioritize finding effective treatments over evaluating single therapy [40].

Conclusions

Using AFsepsis principles, we illustrate the impact of AFsepsis on sample size estimations in sepsis trials. Given that AFsepsis could be substantially less than 100%, estimating AFsepsis based on trial specific eligibility criteria to inform sample size calculations could be another useful additional step in designing sepsis trials. Our results are best considered as proof of concept that requires validation.

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Author contributions

Drs Harrison and Rowan had full access to all the data in the study and take responsibility for integrity of data and the accuracy of the data analyses.

Concept and design: Shankar-Hari, Rubenfeld

Statistical analysis: Shankar-Hari, Harrison

Drafting of manuscript: Shankar-Hari, Rubenfeld

Acquisition, analysis and interpretation of data: All authors

Critical revision of the manuscript for important intellectual content: All authors

Obtained funding: Harrison, Rowan

Administrative, technical, or material support: Rowan, Harrison

Supervision: Rowan, Harrison, Rubenfeld

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Conflict of interest statement:

No conflicts of interest

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Figure legends

Figure-1: Range of AFsepsis estimated using control populations

The fraction of deaths attributable to the sepsis exposure (AFsepsis) = [(Deaths in sepsis – Deaths in non-sepsis)/Deaths in sepsis] ascertained using proportions.

Propensity for sepsis logistic regression models[22] can be used to derive AFsepsis and AFseptic shock. Bar graphs show the mortality difference between sepsis/septic shock compared first to propensity matched ICU-non-sepsis controls and second to age-sex matched general population controls. AF_E = AFsepsis and AFseptic shock respectively; RD = risk difference. Further details of study population and propensity models are provided in Table-1. Model-1 represents propensity model for sepsis. Model-2 represents propensity model for septic shock.

Figure-2: Sample size estimations based on different AFsepsis, effective RRR and control group mortality for sepsis RCTs

The figure shows the sample size estimations for different treatment effectiveness amongst attributable deaths (effective RRR) and different control group mortality for 80% power and 5% alpha. The dot plots are placed at a *fixed* point on all four graphs based on actual RRR used for sample size estimation and sample size per group reported in trials (see eTable-4). Each curve represents a different control group mortality and sample sizes above the curve are adequately powered for the corresponding control group mortality. Each graph represents a different AFsepsis ranging from our lowest estimate of 15% (Figure 2a), median estimate of 54% (Figure 2b) and the highest estimate of 93% (Figure 2c). The maximum overall RRR that is observable if the intervention prevented *all sepsis deaths* in Figure2a is 15%, in Figure 2b is 54% and in Figure2c is 93%, which is equivalent to an effective RRR

of 1.0, that is, the treatment is perfect (effective RRR=1). It is important to highlight using Figure 2d (100% AFsepsis plot) that all these trials were adequately powered across a range of expected mortality under, standard sample size estimation approaches. These graphs also highlight that the sample size requirements will vary by AFsepsis for the same control group mortality.

Figure-3: Illustrating the utility of AFsepsis estimation

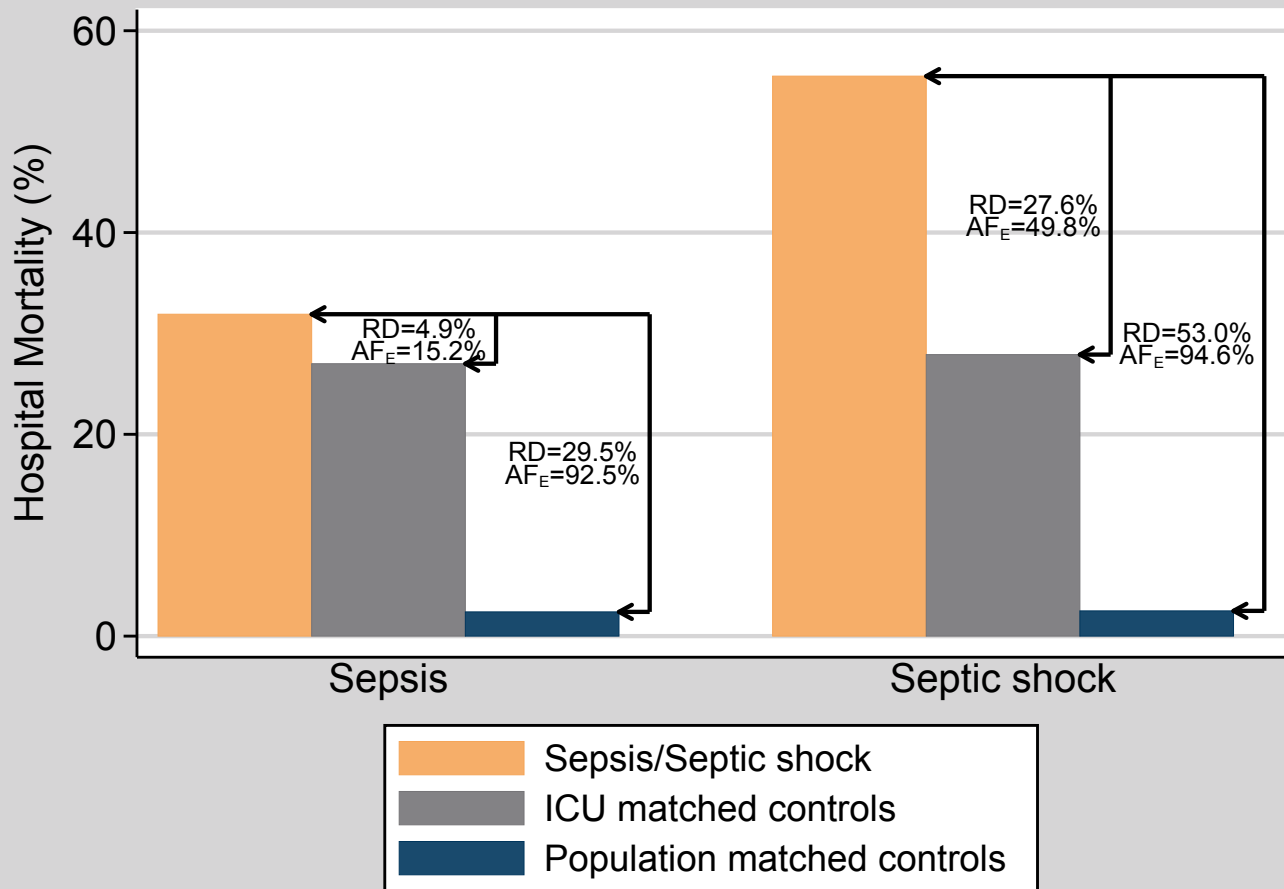
The figure shows the sample size estimations for a fixed control arm mortality (Figure3a=30% and Figure3b=50%). X-axis refers to different treatment effectiveness among the attributable deaths (effective RRR). Y-axis is sample size estimation as a function of changing AFsepsis and effective RRR. Two key principles are highlighted by this figure. First, if we have a fixed control group mortality and a fixed effective RRR, the sample size will increase with decrease in AFsepsis. For example, in a trial with control group mortality of 30% with RRR of 20%, the sample size per group would be 859, 1554, 3554 and 14,437 as AFsepsis in the trial population changes from 100%, to 75%, to 50% and 25% respectively. Second, data from a completed trial and a control population registry can be used to estimate a trial specific AFsepsis to determine the what effective RRR might have been missed. The reason being, with AFsepsis approach, patients' risk of target outcome specifically attributed to sepsis are identified. The notion that there is likely to be trial specific AFsepsis is supported by the higher AFseptic shock shown in Figure-1, explained by differences in septic shock criteria. Abbreviation = relative risk reduction (RRR).

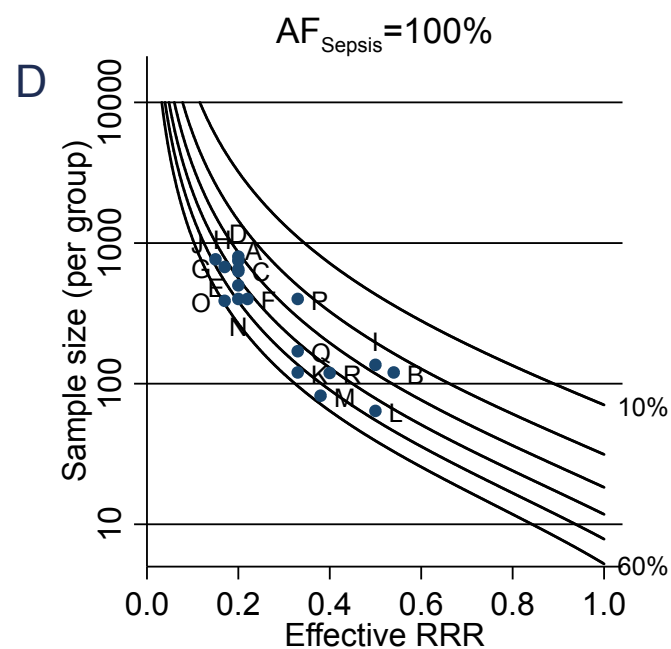
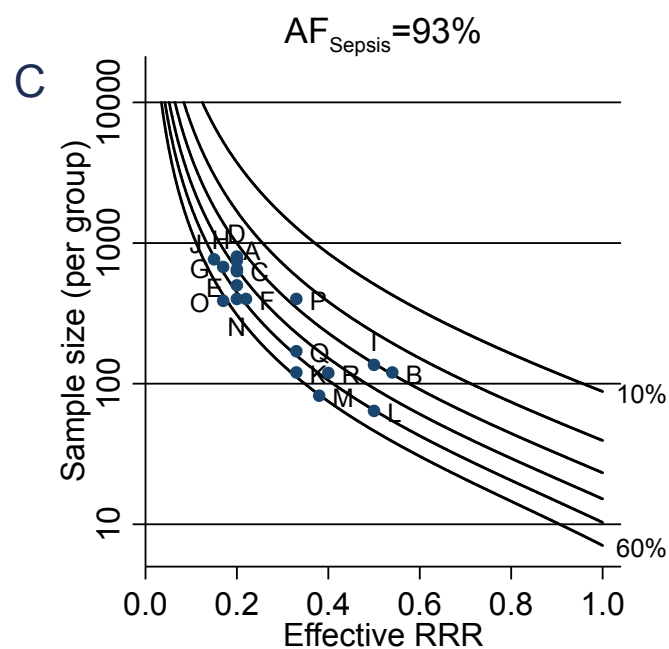
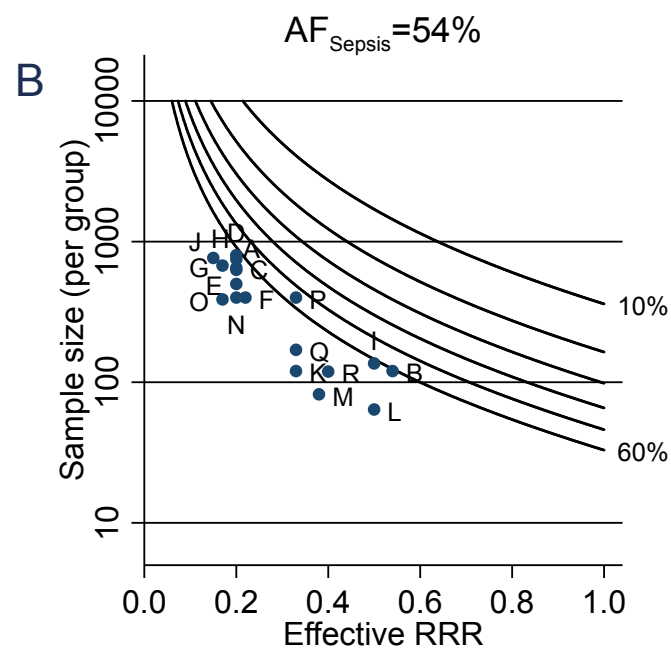
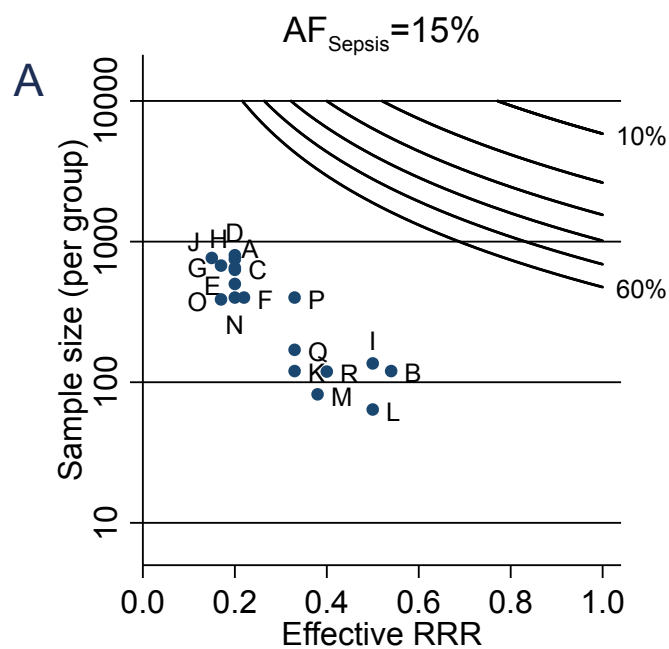
Table legends

Table-1 Baseline characteristics of sepsis, septic shock, and corresponding non-sepsis propensity matched control populations to derive sepsis/septic shock attributable fraction

PMH = past medical history of severe comorbidities; N= number; %= proportion; SD = standard deviation; APACHE II = Acute Physiology And Chronic Health Evaluation II method and score; RD = risk difference; RR = relative risk; 95% CI = 95% confidence interval; Attribution fraction (AF_{sepsis} and $AF_{\text{septic shock}}$); p = p value; std diff = standardised difference between the treated and not treated in propensity models used for balance checking; NMV = not matched variable

Table-2 Control populations and rationale





Trial	Mortality	RRR
A Mouncey PR et al (2015)	40%	20%
B Payen DM et al (2015)	37%	54%
C Yealy DM et al (2014)	30%	20%
D Peake SL et al (2014)	38%	20%
E Holst LB et al (2014)	45%	20%
F Asfar P et al (2014)	45%	22%
G Caironi O et al (2014)	45%	17%
H Ranieri VM et al (2012)	35%	20%
I Huh JW et al (2011)	35%	50%
J De Backer D et al (2010)	43%	15%
K Patel GP et al (2010)	60%	33%
L Palizas F et al (2009)	40%	50%
M Stephens DP et al (2008)	60%	38%
N Sprung CL et al (2008)	50%	20%
O Russell JA et al (2008)	60%	17%
P Werdan K et al (2007)	30%	33%
Q Annane D et al (2007)	60%	33%
R Angstwurm MWA et al (2007)	50%	40%

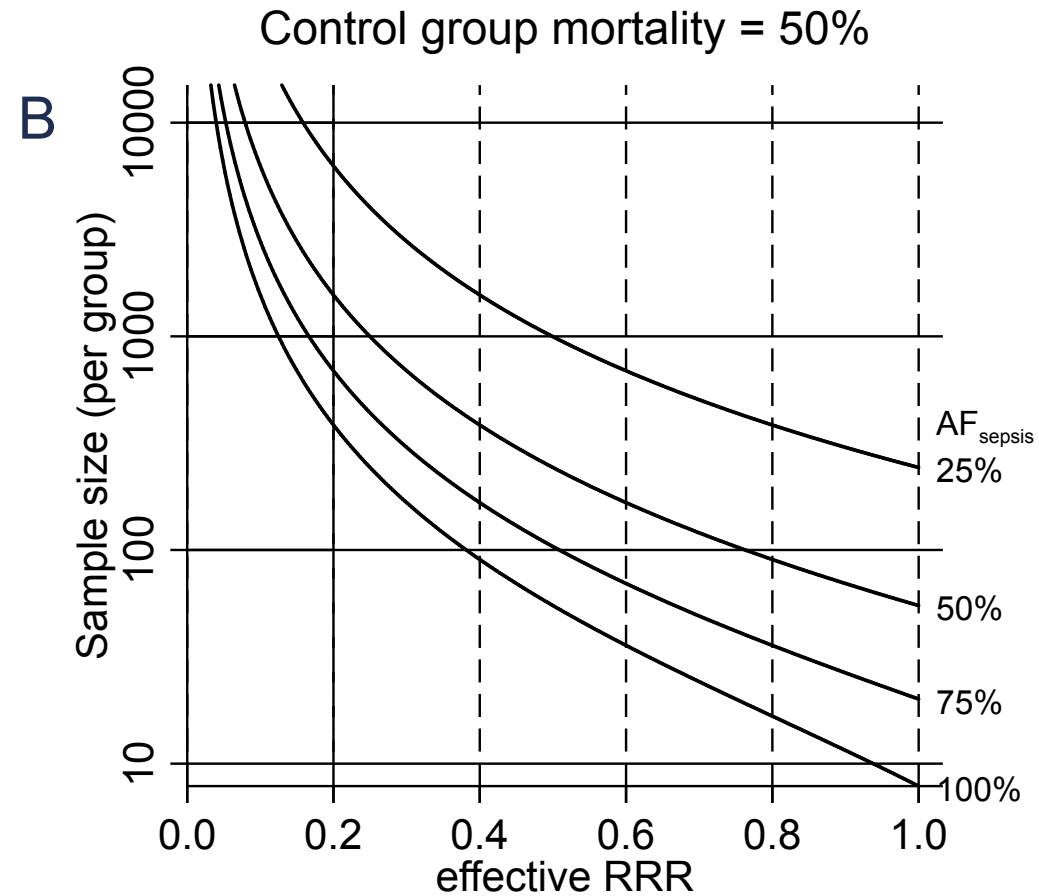
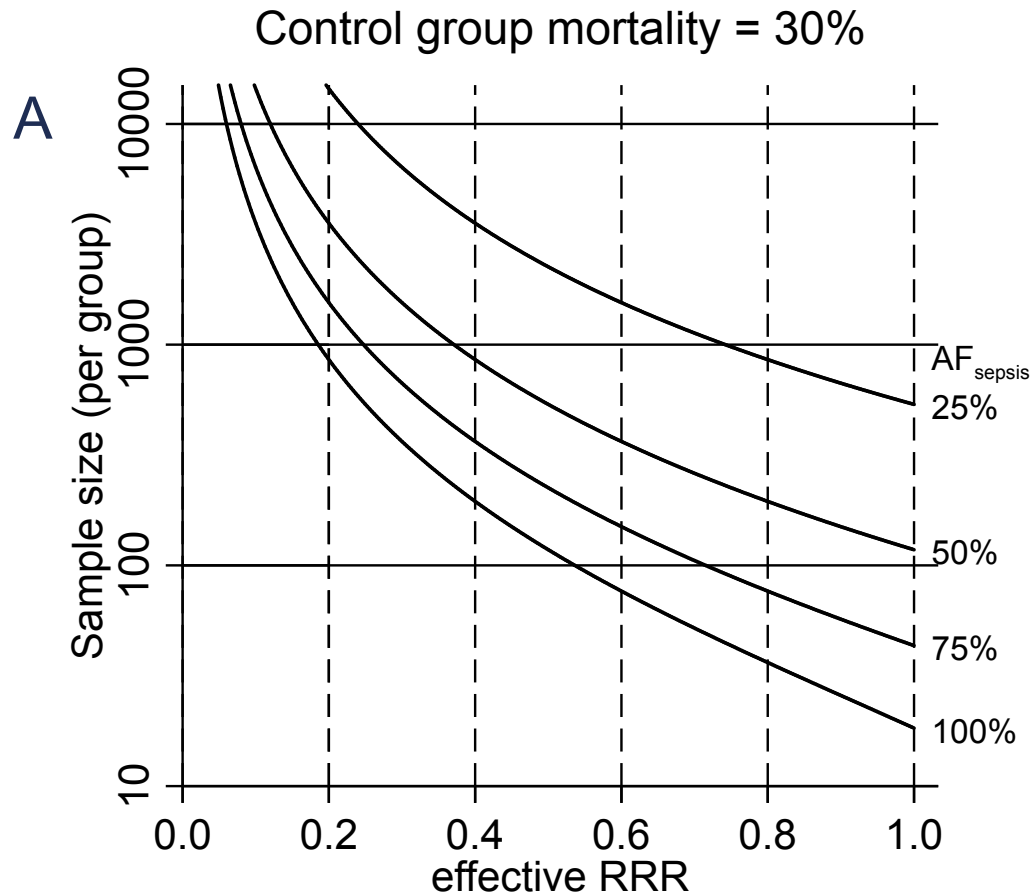


Table-1 Baseline characteristics of sepsis, septic shock, and corresponding non-sepsis propensity matched control populations to derive sepsis/septic shock attributable fraction

	Model-1			Model-2		
Parameter	Sepsis	Non-sepsis	Std Diff	Septic Shock	Non-sepsis	Std Diff
Matched (N; %)	179,704/179,717 (99.9%)			36,833/36,838 (99.9%)		
Age (years; mean (SD))	63.7 (16.4)	63.8 (16.5)	-0.004	65.5 (14.9)	65.5 (14.9)	0.000
Sex Female N (%)	81,553 (45.4%)	81,460 (45.3%)	-0.001	16,556 (45.0%)	16,556 (45.0%)	-0.000
Ethnicity N (%)						
White	162,147 (90.2%)	159,792 (88.9%)	NMV	32,906 (89.3%)	33,069 (89.8%)	NMV
Asian	6,718 (3.7%)	7,213 (4.0%)		1,539 (4.2%)	1,414 (3.8%)	
Black	3,988 (2.2%)	4,625 (2.6%)		813 (2.2%)	853 (2.3%)	
Other	2,082 (1.2%)	2,383 (1.3%)		507 (1.4%)	433 (1.2%)	
Mixed	822 (0.5%)	843 (0.5%)		177 (0.5%)	152 (0.4%)	
Not stated	3,947 (2.2%)	4,848 (2.7%)		891 (2.4%)	912 (2.5%)	
PMH present N (%)	35,988 (20.0%)	35,286 (19.6)	0.010	7,527 (20.4%)	7,527 (20.4%)	-0.000
Comorbidity N (%)						
Cardiovascular	3,097 (1.7%)	4,319 (2.4%)	NMV	662 (1.8%)	769 (2.1%)	NMV
Respiratory	7,777 (4.3%)	4,575 (2.6%)		1,038 (2.8%)	1,259 (3.4%)	
Liver	4,160 (2.3%)	7,454 (4.2%)		1,183 (3.2%)	1,334 (3.6%)	
Renal	3,754 (2.1%)	5,619 (3.1%)		731 (2.0%)	1,037 (2.8%)	
Metastatic disease	4,407 (2.5%)	5,243 (2.9%)		1,000 (2.7%)	1,067 (2.9%)	
Hematologic	6,628 (3.7%)	3,923 (2.2%)		1,558 (4.2%)	1,040 (2.8%)	
Immunosuppressed	14,947 (8.3%)	11,072 (6.2%)		3,241 (8.8%)	2,660 (7.2%)	
Surgical status N (%)						
Medical	135,760 (75.5%)	135,626 (75.5%)	-0.002	27,475 (74.6%)	27,475 (74.6%)	0.000
Elective surgical	7,591 (4.2%)	7,591 (4.2%)		773 (2.1%)	773 (2.1%)	
Emergency surgical	36,353 (20.3%)	36,487 (20.3%)		8,585 (23.3%)	8,585 (23.3%)	
APACHE II Physiology score	13.7 (6.0)	12.2 (6.5)	NMV	17.1 (6.6)	12.5 (6.2)	NMV
APACHE II score	18.5 (6.9)	16.9 (7.4)	NMV	22.1 (7.2)	18.5 (6.9)	NMV
Hospital mortality N (%)	57,319 (31.8%)	48,587 (27.0%)	-	20,439 (55.5%)	10,261 (27.9%)	-
RD (95% CI)	4.9% (4.6% – 5.2%)			27.6% (26.9% – 28.3%)		
RR (95% CI)	1.18 (1.17 – 1.19)			1.99 (1.95 – 2.03)		
AFsepsis or septic shock (%)	15.2% (14.4% – 16.1%)			49.8% (48.8% – 50.7%)		
P - value	<0.001			<0.001		

Table-2: Control populations and rationale

Control description	Comment on control group	Advantages and limitations of control group	Trial design implication for AFsepsis estimate for the control group
ICU non-sepsis controls	<p>This control group represents a broader patient population without sepsis.</p> <p>These patients therefore will have a risk of death that is determined by their illness and risk due to being managed in critical care.</p>	<p>Accounts for the risk of critical care management.</p> <p>Conservative estimate of AFsepsis due to 'risk of death from primary illness that required admission' – provides lower boundary of likely risk reduction, irrespective of the potency of the intervention</p>	<p>Intervention is expected to reduce the risk of death to 'non-sepsis critical illness'.</p> <p>This represents worst case scenario for a new intervention tested in a trial.</p>
Hospitalised infected controls	<p>This control group represents a patient population who have infection but without sepsis.</p> <p>These patients represent, those with either in an earlier stage of illness or do not develop organ dysfunction during the entire hospital stay following an infection.</p>	<p>Accounts for the 'all the dysregulated host response to infection related organ dysfunction' and the risk of death associated with hospitalisation but without the critical care related and infection related risks of death</p> <p>Conceptually elegant model for trial design</p> <p>Probability of any single intervention reducing this magnitude of illness specific risk by altering a single biological mechanism is low</p>	<p>Intervention is expected to reduce the risk of death to that expected in hospitalised infected patients.</p>
Hospitalised non-infected controls	<p>This control group represents a broader patient population who are hospitalised for non-infection reason.</p> <p>These patients therefore will have a risk of death that is determined by their illness and risk due to being managed in hospital.</p>	<p>Accounts for the 'all the dysregulated host response to infection related organ dysfunction, risk of death due to infection and the risk of death associated with hospitalisation but without the critical care related risk of death</p> <p>Probability of any single intervention reducing this magnitude of illness specific risk by altering a single biological mechanism is low</p>	<p>Intervention is expected to reduce the risk of death to that expected in hospitalised non-infected patients</p>
Age and Sex matched general population controls	<p>This control group represents general population risk.</p>	<p>Liberal estimate of AFsepsis as these controls only account for age and sex effects on outcome. As comorbidities are not accounted for, this would be an overestimate of the intervention effect.</p>	<p>Intervention is expected to reduce the risk of death to 'general population, matched on age and sex.</p> <p>This represents best case scenario for a new intervention tested in a trial.</p>

Electronic Supplement Material

Shankar-Hari M, Harrison D, Rowan K, Rubenfeld GD. Estimating attributable fraction of sepsis to inform clinical trials.

eMethods: Further description of study data source and methods

eTable-1: Operationalisation of Sepsis-3 Definitions

Table summarises the operationalisation of Sepsis-3 definitions. This has been recently reporting using the dataset used for this study.

Shankar-Hari M et al. *Epidemiology of sepsis and septic shock in critical care units: comparison between Sepsis-2 and Sepsis-3 populations using a national critical care database* [21].

eTable-2: AFsepsis after excluding patients who had withdrawal of treatment within 12 hours

*AFsepsis and AFseptic shock were estimated using a posthoc sensitivity analysis after excluding patients with active treatment withdrawn 12 hours of ICU admission.

eTable-3: Summary of inclusion and exclusion criteria in the trials identified

eTable-4: Summary of sample size calculations in trials identified to compare with the AFsepsis model

The trials are listed by publication year starting with year 2015. The original reported sample size calculations were extracted and presented in Figure-2 and in this table. We did not use the reported adjustments during interim analyses. RRR was estimated using reported sample size calculations when not explicitly stated. *Lower limit of reported range was used to estimate RRR from 6% - 7% absolute risk reduction used in the trial to estimate sample size. Display code – identifies the trial in Figure-2. RRR = relative risk reduction; EGDT = Early goal directed therapy; Hb = Hemoglobin; Proportions were rounded to whole numbers without decimals.

eFigures:

eFigure-1: Flow diagram for patients in the study

eFigure-2: Flow diagram for trial selection

eMethods: Further description of study data source and methods

For sepsis cases and non-septic critically ill controls, we used the consecutive admissions between January 2011 and December 2015 recorded in the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme Database (CMPD) [22]. The ICNARC-CMPD is the national clinical audit for adult general ICUs in England. For consecutive ICU admissions, trained data collectors collect sociodemographic, comorbidity, and physiologic data to precise rules and definitions, during the first 24 hours following admission to ICU. Diagnostic data are determined clinically and coded using the hierarchical ICNARC Coding Method with 5 tiers [22]. A code is automatically generated that represents a patient's clinical diagnosis route through this hierarchy. Collected data undergo extensive local and central validation prior to pooling into the CMPD. The CMPD has been independently assessed to be of high quality. Support for the collection and use of these data has been obtained under Section 251 of the National Health Service Act 2006 (PIAG 2–10(f)/2005).

Additional details of propensity models

We used nearest neighbour 1:1 greedy matching without replacement with caliper bandwidth specified as 0.1 standard deviation of the propensity score to generate a conditional probability of sepsis [23]. We checked balance of all the matched covariates using standardized differences of mean [23].

Rationale for sensitivity analysis

As a sensitivity analysis and to reflect frequent exclusion criteria in clinical trials, we ascertained AFsepsis and AFseptic shock in patients without severe comorbidities using propensity models with age, sex, and surgical status as covariates to confirm our assumption that comorbidity effect is accounted for by the main propensity model, by excluding all patients with comorbidities from the analysis set prior to deriving these models. We conducted a post hoc sensitivity analysis excluding patients who had withdrawal of treatment decision made within 12 hours of ICU admission. The rationale being that these patients would be excluded from sepsis and septic shock clinical trials.

eTable-1: Operationalisation of Sepsis-3 Definitions

Criteria	Sepsis-3
Infection	Reason for ICU admission
Organ dysfunction	SOFA score of 2 or more in any one organ system or SOFA score of one in two or more organ systems
Sepsis	Sepsis = Infection AND ≥ 2 SOFA points
Septic shock	Infection AND cardiovascular SOFA ≥ 2 AND serum lactate concentrations > 2 mmol/L

eTable-2: AFsepsis and AFseptic shock after excluding patients who had withdrawal of treatment within 12 hours

Parameter	Sepsis N = 179,700	Non-sepsis N=179,702	Septic Shock N=36,832	Non-sepsis N=36,833
Withdrawal of treatment N (%)	24,427 (13.6%)	19,963 (11.1%)	10,197 (27.7%)	4,034 (11.0%)
Time to withdrawal of treatment median (IQR) days	2.9 (1.0 – 7.8)	2.1 (0.8 – 4.9)	2.5 (1.0 -7.2)	2.5 (0.9 – 5.9)
Withdrawal of treatment within 12 hours of ICU admission N (%)	3,077 (1.7%)	2,923 (1.7%)	1,188 (3.2%)	563 (1.5%)
*RD (95% CI)	7.4% (6.7% – 8.1%)		29.4% (27.9% – 31.0%)	
*RR (95% CI)	1.21 (1.19 – 1.23)		1.80 (1.74 – 1.87)	
*AFsepsis or septic shock (%)	17.2% (15.7% – 18.9%)		44.5% (42.6% – 46.4%)	
P - value	< 0.001		< 0.001	

eTable-3: Inclusion and exclusion criteria in the trials identified

N	Trial ID	Inclusion criteria	Exclusion criteria
1	Mouncey PR et al (2015)[8]	Adults (≥18 years of age) were eligible if within 6 hours after presentation to the emergency department they had a known or presumed infection, two or more criteria of the systemic inflammatory response syndrome, and either refractory hypotension (systolic blood pressure, <90 mm Hg; or mean arterial pressure, <65 mm Hg, despite resuscitation with at least 1 litre of intravenous fluids within 60 minutes) or hyperlactatemia (blood lactate level, ≥4mmol per litre)	Age less than 18 years; pregnancy; Primary diagnosis of: acute cerebral vascular event, acute coronary syndrome, acute pulmonary oedema; status asthmatics; major cardiac arrhythmia (as part of primary diagnosis); seizure; drug overdose; injury from burn or trauma; hemodynamic instability due to active gastrointestinal haemorrhage; Requirement for immediate surgery; Known history of AIDS; Do-not-Attempt-Resuscitation (DNAR) order; Advanced directives restricting implementation of the resuscitation protocol; Contradiction to: central venous catheterization or to blood transfusion; Attending clinician deems aggressive resuscitation unsuitable; Transferred from another in-hospital setting; Not able to commence resuscitation protocol within one hour of randomization or complete six hours of protocol treatment from commencement
2	Payen DM et al (2015)[3]	Patients with severe sepsis or septic shock and underwent emergency surgery to treat visually confirmed peritonitis. In order to distinguish between hypotension resulting from the effect of sedation, shock had to occur or persist within 10 h after surgical procedure with a duration of at least 2 h. Shock was classically defined as a hypotension resistant to fluid administration requiring norepinephrine or other vasopressor	Age < 18 years; protected adult under law; Pregnancy; Moribund status or life expectancy lower than 48h; Aplasia related to chemotherapy or malignancy; Non-surgically treated abdominal sepsis; Absence of intra-abdominal organ perforation ; A mesenteric ischemia without perforation; Trauma-induced gastro-intestinal perforation; Appendiceal peritonitis; A cirrhosis Child C; A prolonged cardiac arrest within 72 hours before surgery; A contraindication to the use of heparin for hemoperfusion (risk of bleeding and / or history of heparin induced thrombocytopenia); Discovery of an advanced stage of cancer; Additionally, the patients who refused to participate even after inclusion by the emergency process and who refused to participate after recovery were excluded from the study analysis.
3	Yealy DM et al (2014)[11]	We recruited patients in the emergency department in whom sepsis was suspected according to the treating physician, who were at least 18 years of age, who met two or more criteria for systemic inflammatory response syndrome and who had refractory hypotension or a serum lactate level of 4 mmol per liter or higher.	Patients who had: a primary diagnosis of acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, major cardiac arrhythmia, active gastrointestinal hemorrhage, seizure, drug overdose, burn or trauma; a requirement for immediate surgery; a known CD4 count <50/mm ² ; an advance directive that would restrict protocol implementation; a contraindication to central venous catheterization; a high likelihood of refusing blood transfusion (e.g., Jehovah's Witness); a treating physician who deemed resuscitation to be futile; on-going participation in another interventional study; known pregnancy, or; been transferred from another hospital.
4	Peake SL et al (2014)[10]	Eligibility criteria were a suspected or confirmed infection, two or more criteria for a systemic inflammatory response and evidence of refractory hypotension or hypoperfusion. Refractory hypotension was defined as a systolic blood pressure of less than 90 mm Hg or a mean arterial pressure of less than 65 mm Hg after an intravenous fluid challenge of 1000 ml or more administered within a 60-minute period. Hypoperfusion was defined as a blood lactate level of 4.0 mmol per liter or more.	Patients were not eligible for enrolment if they met one or more of the following criteria: age < 18 years; contraindication to central venous catheter insertion in the superior vena cava; contraindication to receiving blood products; hemodynamic instability due to active bleeding; underlying disease process with a life expectancy < 90 days; death deemed imminent and inevitable; documented limitation of therapy order restricting implementation of the study protocol or aggressive care deemed unsuitable by the treating clinician; in-patient transfer from another acute health care facility; confirmed or suspected pregnancy; inability to commence EGDT within one hour of randomization or deliver EGDT for 6 hours
5	Holst LB et al (2014)[9]	(1) At least 2 SIRS criteria; AND (2) suspected focus of infection as either: An organism grown in blood or sterile site OR An abscess or infected tissue (e.g. pneumonia, peritonitis, urinary tract, vascular line infection, soft tissue, etc). AND (3) hypotension (Systolic blood pressure < 90 mmHg or mean arterial pressure < 70 mmHg) despite fluid therapy OR vasopressor/inotrope infusion to maintain blood pressure.	Documented wish against transfusion OR Previous serious adverse reaction with blood products, excl. transfusion-associated circulatory overload OR Presence of acute myocardial ischemia OR (defined as: patients diagnosed with <i>acute myocardial infarction</i> (ST-elevation myocardial infarction or non-ST elevation myocardial infarction) or <i>unstable angina pectoris</i> during current hospital admission, according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischemic signs on ECG, clinical presence) AND the patient has received treatment,

			initiated during current hospital admission, as a consequence of this (reperfusion strategies (PCI/thrombolysis) or initiation/increased antithrombotic treatment)). Life-threatening bleeding OR (defined as: (1) Presence of hemorrhagic shock, as judged by research or clinical staff. OR (2) the need for surgical procedure, incl. endoscopy to maintain hemoglobin levels); Red cell transfusion during current ICU admission OR Withdrawal from active therapy or brain death OR Acute burn injury - regardless of degree and burn surface area OR Lack of informed consent
6	Afzar P et al (2014)[13]	<p>Presence of septic shock within less than 6 hours (onset defined by the time of introduction of catecholamines)</p> <p>A minimum vasopressor infusion rate of 0.1 µg/Kg/min</p> <p>The criteria for septic shock were the official criteria of the American College of Chest Physicians / Society of Critical Care Medicine, i.e.:</p> <p>sepsis: patients with a systemic inflammatory response syndrome plus a suspected or Septic shock was defined as sepsis plus arterial hypotension (systolic blood pressure < 90 mm Hg) refractory to fluid resuscitation (minimum 30 mL/kg within 6 hours prior to the start of catecholamines) and requiring vasopressor support. The consent of the subject was obtained from the patient if his or her condition permitted, from family or person of trust if present. As last recourse, the procedure for inclusion in emergency situations was applied in the absence of the family or next of kin.</p>	"Legally protected" adult patient., (i.e. These patients are protected by law and cannot be included in RCT e.g. patients who have no guardian, are convicted felons and in jail etc.; Person not affiliated with or non-beneficiary of a health care system.; Minors and pregnant women; Patient currently in an exclusion period following participation in another biomedical study; Participation in another interventional study with "28 day mortality" as primary endpoint or one of the secondary endpoints of SEPSISPAM; Decision. not to resuscitate.
7	Caironi O et al (2014)	Proved or suspected infection in at least one site: a) lung; b) abdomen; c) genito-urinary tract; d) other (blood, skin and soft tissue, central nervous system, bones and joints, cardiac system, catheter-related infection, other AND two or SIRS criteria AND Presence of at least a severe and acute sepsis-related organ dysfunction, as measured by the modified Sequential Organ Failure Assessment (SOFA) score of 1 or more on any one of the organ systems	Age below 18 years; Terminal state; Known adverse reaction to albumin administration; Severe sepsis or septic shock in patients after proved or suspected head injury, clinically Active; Congestive heart failure (New York Heart Association class of 3 or 4); Pathological conditions in which albumin administration is clinically indicated (hepatic cirrhosis with ascites, intestinal malabsorption syndrome, nephrotic syndrome, burns); More than 24 hours since inclusion criteria were met; Religious objection to the administration of human blood products; Inclusion in other experimental studies
8	Ranieri VM et al (2012)[17]	<p>Inclusion criteria to obtain informed consent = 1. Aged C 18 years old; 2. Must have an infection requiring intravenous antimicrobial therapy; 3. Must meet at least two of the four systemic inflammatory response syndrome (SIRS) criteria. 4. Must have septic shock, defined as:</p> <p>(a) The patient must have received intravenous fluid resuscitation of C 30 mL/kg administered within the time period spanning the 4 hours before and 4 hours after initiation of vasopressor therapy. (b) The patient must have a continuous requirement for at least one of the vasopressors listed below at the dose shown below for at least four hours: Norepinephrine C 5 mcg/min Dopamine C 10 mcg/kg/min Phenylephrine C 25 mcg/min Epinephrine C 5 mcg/min Vasopressin C 0.03 units/min ; (c) The patient must meet at least 1 of the following criteria consistent with hypoperfusion during the 36 hours prior to study entry: Metabolic acidosis: base deficit C 5.0 mmol/L or venous bicarbonate \ 18 mmol/L or lactate C 2.5 mMol/L. Urine output \ 0.5 mL/kg h-1 for 1 hour or a 50% increase in creatinine from a known baseline level. Acute hepatic dysfunction: AST or ALT [500 IU/dL or bilirubin [2 g/dL. Inclusion criterion to proceed to randomisation 5. Patients must remain vasopressor dependent throughout the pretreatment period and through the time of randomisation with the goal of maintaining a systolic blood pressure of approximately 90 mm Hg or higher or a mean arterial pressure of 65 mm Hg or higher with reasonable attempts made to wean the patient from vasopressor support, if applicable. (Note: dopamine at doses \ 5 mcg/kg/min does not fulfil the criteria for vasopressor dependency.)</p>	< 18 years of age; Does Not Have Evidence of Infection; Does Not Satisfy SIRS Criteria; Does Not Meet Septic Shock Criteria; Has Not Remained Vasopressor Dependant; Vasopressor Therapy for > 24 Hours; Sepsis Induced Organ Dysfunction > 36 Hours; Single Organ Dysfunction and Recent Surgery (within last 30 days); Post-op < 12 hours, Evidence of Bleeding, or Planned Surgery; Platelet Count < 30x 10 ⁹ /L; INR > 5.0; Active Internal Bleeding or Increased Risk for Bleeding; Receiving or Concurrent Need for Bleeding Risk Medications; Not Expected to Survive 28 Days due to Pre-existing Condition; Moribund & Death is Perceived to be Imminent; Not Committed to Aggressive Management; Received DrotAA within Last 30 Days; Pregnant or Lactating & the Milk is to be Ingested by the Newborn; Fail to Give Written Informed Consent; Participating in Competing Study of Investigational Drug; Incomplete Information available; Condition Improving; Second Sepsis Episode; Site On Hold; Pharmacy Issue; Not in ICU (Monitored Unit)
9	Huh JW et al (2011)[20]	Onset of septic shock within 6 h and relative adrenal insufficiency, defined as an increase in cortisol level of <9 mg/dL or a basal cortisol level of <25 mg/dL.	Advanced cancer, immunosuppression, previous treatment with corticosteroids, refusal of the attending staff or patient family and absence of adrenal insufficiency

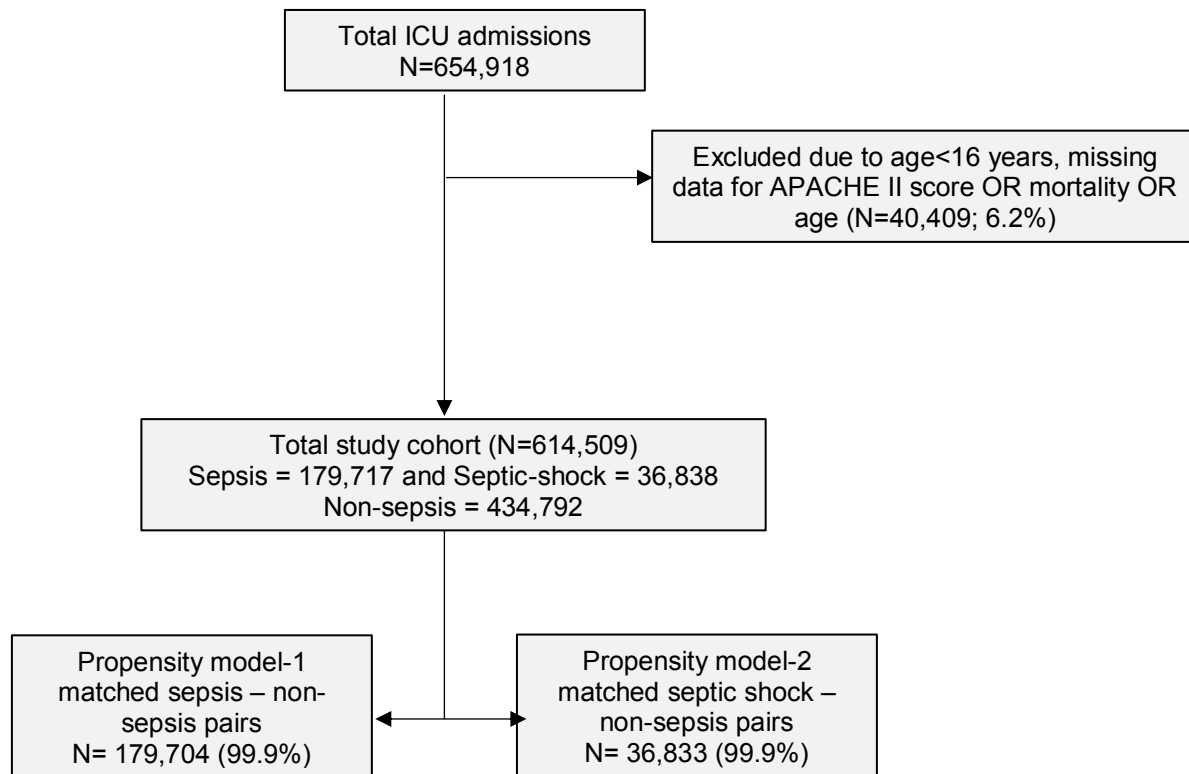
10	De Backer D et al (2010)[19]	All patients 18 years of age or older in whom a vasopressor agent was required for the treatment of shock were included in the study.	Patients were excluded if they were younger than 18 years of age; had already received a vasopressor agent (dopamine, norepinephrine, epinephrine, or phenylephrine) for more than 4 hours during the current episode of shock; had a serious arrhythmia, such as rapid atrial fibrillation (>160 beats per minute) or ventricular tachycardia; or had been declared brain-dead.
11	Patel GP et al (2010)[4]	Eligible patients had to be in shock (MAP <60 mmHg and/or systolic blood pressure <90 mmHg) after adequate fluid resuscitation, as determined by a CVP greater than 8 mmHg for non-mechanically ventilated patients (12 to 15 mmHg for patients requiring mechanical ventilation) and require the administration of a vasopressor for management.	Patients were excluded from the study if they were found to have alternative causes of their shock (i.e., hypovolemic, haemorrhagic, cardiogenic, anaphylactic, and/or obstructive shock) or another cause of their SIRS. Patients who were allergic to DA or NE were excluded, as were patients who were on vasopressors for more than 6 h before enrolment.
12	Palizas F et al (2009)[5]	All adult patients fulfilling criteria for septic shock according to the ACCP/SCCM Consensus Conference within 48 hours of ICU admission were considered and selected if they were in a 12-hour time window.	Exclusion criteria were: terminal illness with the patient expected to die within 28 days, irreversible neurologic impairment, and contraindication for nasogastric tube placement.
13	Stephens DP et al (2008)[6]	Septic shock was defined according to the ACCP/SCCM Consensus Conference criteria and included the presence of sepsis, shock, and evidence of at least one other organ dysfunction. The inclusion criteria were adult patients (18 yrs of age) admitted to the ICU that met these criteria for septic shock who were assessed for eligibility within 24 hrs of meeting these criteria. The time from screening to consent and study drug administration was limited to 36 hrs.	Patients with culture-confirmed melioidosis, hematologic malignancy, febrile neutropenia, myelodysplasia or congenital neutropenia, splenomegaly, acute myocardial infarction in the previous 24 hrs, pregnancy, known hypersensitivity to G-CSF, known objection to participation, previous transplantation, active orders limiting treatment, and patients with an expected survival of 24 hrs, patients previously enrolled or who had received G-CSF within the previous month.
14	Sprung CL et al (2008)[15]		
15	Russell JA et al (2008)[12]	Patients older than 16 years of age who had septic shock that was resistant to fluids (as defined by lack of response to 500 ml of normal saline or a requirement for vasopressors) and low-dose norepinephrine were considered for enrolment.	unstable coronary syndrome (acute myocardial infarction during this episode of shock based on the combination of history, electrocardiogram, and enzyme changes (as defined by investigator); greater than 24 hours had elapsed since the patient met entry criteria; use of open-label vasopressin for blood pressure support during the current hospital admission; malignancy or other irreversible disease or condition for which six-month mortality was estimated to be $\geq 50\%$; acute mesenteric ischemia either proven or suspected. A patient could be excluded by the investigator if, in their judgment, the condition was strongly suspected but not proven by conventional criteria or the attending physician had initiated presumptive therapy, death anticipated within 12 hours; underlying chronic heart disease (NYHA class III or IV) and shock; physician and team were not committed to aggressive care; severe hyponatremia (serum sodium < 130 mmol/L); traumatic brain injury (GCS < 8 prior to onset of sepsis); Raynaud's phenomenon, systemic sclerosis or vasospastic diathesis, pregnancy (positive serum β -HCG).
16	Werdan K et al (2007)[14]	Four of nine positive sepsis criteria: Temperature; White blood cell count 12 G/L or 3.5 G/L Heart rate >100 beats/min; Respiratory rate >28 breaths/min or $\text{FIO}_2 > 0.21$; Mean arterial pressure <75 mm Hg; In case of invasive hemodynamic monitoring (not obligatory for study participation), cardiac index 4.5 L/min/m ² or systemic vascular resistance 800 dyne/sec/cm ⁵ Platelets <100 G/L; Positive blood cultures; Clinical evidence of sepsis (surgical or invasive procedure during the preceding 48 hrs or presence of an obvious septic focus); A sepsis score of 12–27, rating several variables categorized into four classes according to Elebute and Stoner: local signs of infection, pyrexia, organ failure, and laboratory values 3. An APACHE II score of 20–35 as a measure of the degree of disease severity	Not provided with the main paper. Readers are referred to a previous publication 10 years ago – by Pilz G, Fateh-Moghadam S, Viell B, et al: Supplemental immunoglobulin therapy in sepsis and septic shock—Comparison of mortality under treatment with polyvalent i.v. immunoglobulin versus placebo. Protocol of a multicenter, randomized, prospective, double-blind trial. Theor Surg 1993; 8:61–83
17	Annane D et al (2007)[16]	evidence of infection; at least two of the four criteria for systemic inflammatory response syndrome (temperature above 38°C or below 36°C, heart rate above 90 bpm, respiratory rate above 20 cycles per min and arterial CO ₂ tension below 32 mm Hg or need for mechanical ventilation, polymorphonuclear neutrophil count above 12×10^9 cells per L or below 4×10^9 cells per L); and at least two signs of tissue hypoperfusion or organ dysfunction. These signs were defined as a ratio of arterial oxygen tension over inspired fraction of oxygen of less than 280 mm Hg (if patient was mechanically ventilated), urinary output below 0.5 mL per kg of bodyweight per h or below 30 mL/h (for at least 1 h), or arterial lactate concentration above 2 mmol/L, platelet count below 100×10^9 cells per L. Additionally, patients had to meet the three following criteria for less than 24 h: systolic blood pressure below 90 mm Hg or mean blood pressure below 70 mm	Reasons for exclusion were pregnancy; evidence of obstructive cardiomyopathy, acute myocardial ischaemia, or pulmonary embolism; advanced stage cancer, haematological malignancy, or AIDS with a decision to withhold or withdraw aggressive therapies; persistent (longer than a week) polymorphonuclear neutrophil count of less than 0.5×10^9 cells per L; and inclusion in another clinical trial.

		Hg; administration of fluid bolus of at least 1000 mL or capillary wedge pressure between 12 and 18 mm Hg; and need for more than 15 µg per kg of bodyweight per min of dopamine or any dose of epinephrine or norepinephrine.	
18	Angstwurm MWA et al (2007)[7]	Males and females >18yrs with an Acute Physiology and Chronic Health Evaluation (APACHE) III score (22) 70 and at least two of the following criteria (23): Rectal body temperature >38°C or hypothermia <36°C; Heart rate >90 beats/min; Respiratory frequency >20 and PaCO ₂ mm Hg >4.3 kPa; Leukocytes 12,000/ L or 4 000/ L or 10% immature leukocytes; Decrease of platelet count 50% within the first 24 hrs or platelets 150,000/ L at admission; Admission into the study after diagnosis within 24 hrs; Beginning of treatment within 1 hr after inclusion; Informed consent either from the patient or the relative/close friend	Pregnancy; Missing informed consent of the patient or the relative/intimate friend of the patient; Withdrawal of informed consent by patient or next of kin after inclusion into the study; Participation in any other clinical trial currently or within the last 30 days; Prior participation in this clinical trial; Cerebral injury due to hypoxia after cardio- pulmonary resuscitation; Primary concomitant disease with an expected high mortality within 2 months; Do-not-resuscitate code; Malignant primary disease as the cause of SIRS or sepsis, for example, agranulocytosis as a result of chemotherapy or idiopathic bone marrow aplasia; Hemorrhagic-necrotizing pancreatitis with- out infectious complications

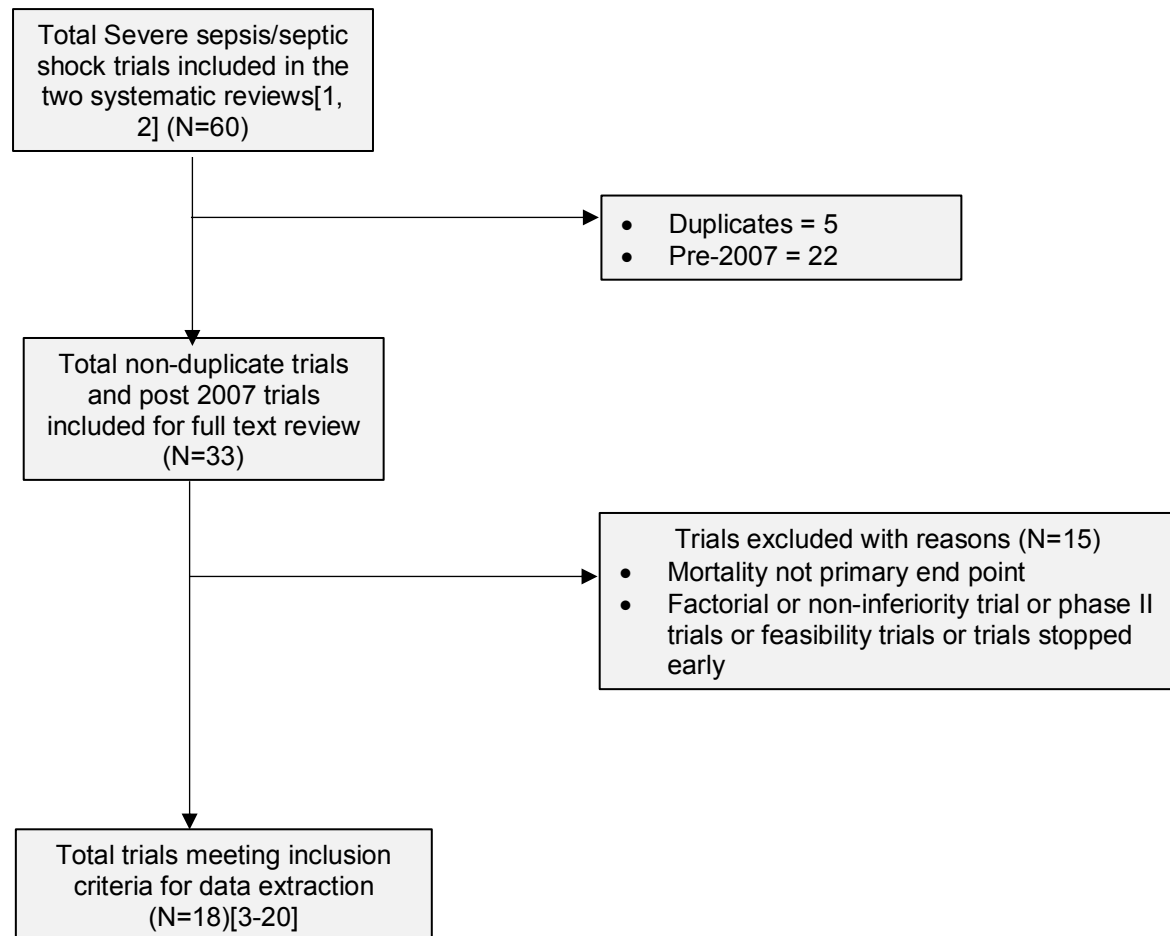
eTable-4: Trials identified to illustrate the AFsepsis model

N	Trial ID	Control group	Intervention group	Code	Mortality time point	Control group mortality	RRR	Power	Alpha	Sample size per group
1	Mouncey PR et al (2015)[8]	Standard care	EGDT	A	90-day	40%	20%	80%	5%	630
2	Payen DM et al (2015)[3]	Standard care	Polymyxin B hemoperfusion	B	28-day	37%	54%	94%	4.5%	120
3	Yealy DM et al (2014)[11]	Standard care*	EGDT	C	60-day	30% - 46%*	20%	80%	5%	650
4	Peake SL et al (2014)[10]	Standard care	EGDT	D	90-day	38%	20%	85% - 90%	5%	800
5	Holst LB et al (2014)[9]	>7g/L Hb target	>9g/L Hb target	E	90-day	45%	20%	80%	5%	500
6	Afzar P et al (2014)[13]	65 – 70mmHg MAP target	80 – 85mmHg MAP target	F	28-day	45%	22%	80%	5%	400
7	Caironi O et al (2014)	Standard care	Albumin>30g/L	G	28-day	45%	17%	80%	5%	675
8	Ranieri VM et al (2012)[17]	Placebo	Activated protein C	H	28-day	35%	20%	80%	5%	750
9	Huh JW et al (2011)[20]	3-day hydrocortisone	7-day hydrocortisone	I	28-day	35%	50%	80%	5%	136
10	De Backer D et al (2010)[19]	Dopamine	Nor-epinephrine	J	28-day	43%	15%	80%	5%	765
11	Patel GP et al (2010)[4]	Dopamine	Norepinephrine	K	28-day	60%	33%	80%	5%	120
12	Palizas F et al (2009)[5]	CI>3.0L/min/m2	Intramucosal pH>7.32	L	28-day	40%	50%	80%	5%	64
13	Stephens DP et al (2008)[6]	Placebo	G-CSF	M	Hospital	60%	38%	80%	5%	82
14	Sprung CL et al (2008)[15]	Placebo	Hydrocortisone	N	28-day	50%	20%	80%	5%	400
15	Russell JA et al (2008)[12]	Nor-epinephrine	Vasopressin	O	28-day	60%	17%	80%	5%	388
16	Werdan K et al (2007)[14]	Placebo	IVIg	P	28-day	30%	33%	90%	5%	400
17	Annane D et al (2007)[16]	Epinephrine	Nor-epinephrine + Dobutamine	Q	28-day	60%	33%	95%	5%	170
18	Angstwurm MWA et al (2007)[7]	Standard care	Selenium	R	28-day	50%	40%	80%	5%	119
	Summary statistics	-	-	-	-	44% (37% - 50%)	20% (20% - 38%)	-	-	-

eFigure-1: Flow diagram for patients in the study



eFigure-2: Flow diagram for trial selection



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